New biocompatible polymeric systems carrying triflusal or HTB.

The present invention relates to a new series of biocompatible polymeric systems, and more specifically to a new series of biocompatible polymeric systems carrying triflusal or HTB. The invention also relates to a process for their preparation, as well as to their uses, particularly as coatings for prostheses.

Background of the invention

The use of synthetic biomaterials in the field of cardiovascular surgery and particularly in the reconstruction of the vascular system has been one of the greatest advances in this field. The materials used must not only possess suitable physicochemical properties such as flexibility, hydrolytic stability and fatigue strength, but it is essential that they exhibit a good blood biocompatibility or hemocompatibility. The contact of the prosthetic devices with the blood flow leads to the deposition of plasmatic proteins on the surface of the biomaterial and to the activation of the coagulation cascade, generating a thrombogenic surface.

No material has yet been found that can be regarded in a strict sense as non-thrombogenic, although certain materials have been used with success in the manufacture of big-diameter (> 6 mm) vascular prostheses. Thus, for example, during the last decades commercially available synthetic vascular grafts based mainly on meshes woven or knitted with polyester (Dacron®), polyamide (Nylon®) or polytetrafluoroethylene (PTFE, Teflon®) fibres as well as porous, expanded PTFE (Goretex®) systems have been used. Whereas this type of prostheses works relatively well when used to substitute big-diameter vessels, the failure rate is quite high when they are used to substitute small- or medium-calibre vessels at short or medium term due to the appearance of thrombosis. It is therefore still necessary to improve the biomaterials used up to now for this kind of applications.

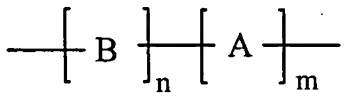
Triflusal, whose chemical name is 2-acetyloxy-4-trifluoromethylbenzoic acid, is a platelet aggregation inhibitor marketed for the treatment of thromboembolic disorders. Its main metabolite, known by the acronym HTB and whose chemical name is 2-hydroxy-4-trifluoromethylbenzoic acid, also exhibits a remarkable platelet aggregation-inhibitory activity. Both compounds are disclosed in the patent US 4,096,252.

The present invention provides a new series of biocompatible polymeric derivatives carrying triflusal or HTB, which, when used as coatings for the surface of prostheses, improve the thrombogenic properties of said devices because they

carry compounds with platelet aggregation-inhibitory activity.

Description of the invention.

The present invention relates to a polymeric compound of relative general formula I



(I)

wherein:

A represents a residue of an acrylic or vinylic monomer carrying triflusal or HTB, wherein triflusal or HTB are linked to the remainder of the monomer molecule through an *in vivo* hydrolizable covalent bond;

B represents a residue of a second polymerisable monomer;

m and n represent the molar fractions of the monomers A and B in the polymer so that m + n is always 1 and m is always different from 0;

and wherein the A and B units are distributed randomly in the polymer.

The present invention also relates to a process for the preparation of a polymeric compound of formula I which comprises the radical polymerization of a monomer A and optionally a second monomer B in the molar fractions m and n, respectively, in the presence of a polymerization initiator, in a suitable solvent.

As mentioned above, the polymeric compounds of the present invention are useful as coatings for the surface of synthetic biomaterials. Due to the fact that the polymers of the present invention carry triflusal or HTB, compounds with a remarkable antiaggregating activity, which are gradually released through the hydrolysis of the covalent bond that links them to the rest of the polymeric system, the application of the polymers of the present invention on the surface of synthetic biomaterials improves the thrombogenic properties thereof. The polymeric compounds of the present invention are specially suited to coat vascular prostheses, particularly those of small or medium calibre, as well as artificial cardiac valves.

The present invention therefore also relates to the use of a polymeric compound of formula I as coating for synthetic biomaterials, and particularly as coating for vascular prostheses and artificial cardiac valves.

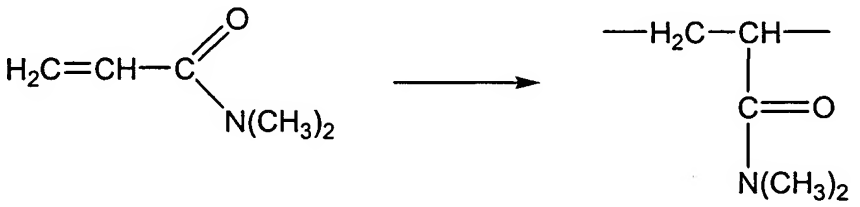
The invention further relates to the use of triflusal or HTB for the

preparation of biocompatible polymeric compounds for coating synthetic biomaterials, particularly vascular prostheses and artificial cardiac valves.

The present invention further relates to a synthetic biomaterial coated with a polymer carrying triflusal or HTB of formula **I**, and particularly to vascular prostheses and artificial cardiac valves coated with a polymer carrying triflusal or HTB of formula **I**.

In the polymeric compounds of the present invention triflusal or HTB are linked to the rest of the polymeric system through hydrolyzable covalent bonds. As mentioned above, triflusal or HTB are gradually released through the hydrolysis of said covalent bonds. Due to this, the polymeric compounds of the present invention can also be used as controlled delivery systems for triflusal or HTB. The present invention therefore also relates to the use of a polymeric compound of formula **I** as a controlled delivery system for triflusal or HTB, having utility in therapy.

Throughout the present specification and particularly in formula **I**, the term residue of a polymerisable monomer, whether acrylic, vinylic or of a different type, shall be understood as the residue resulting from the polymerization of the corresponding monomer. Thus, for example, when the polymerisable monomer corresponding to B is N,N-dimethylacrylamide, in formula **I** B represents in fact the residue of said monomer once polymerized, as shown below:



"polymerisable monomer precursor of B in formula I"

"B (residue of the monomer after polymerization)"

Unless otherwise specified, the nomenclature A and B will be used throughout the present specification to refer without distinction to the polymerisable monomer or to the corresponding polymerized residue in the polymer of formula **I**.

In formula **I**, A represents a residue of any acrylic or vinylic monomer carrying triflusal or HTB. The expression "carrying trifusal or HTB" means that the

monomer comprises a molecule of triflusal or HTB linked to the rest of the acrylic or vinylic moiety through a covalent bond that is hydrolyzable *in vivo*, that is under physiological conditions.

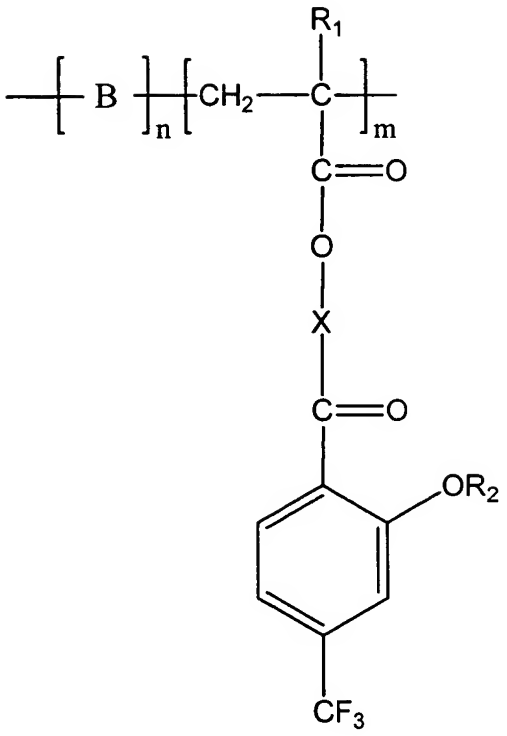
With regard to B, this represents a residue of a second polymerisable monomer, so that when B is present in a polymeric compound of formula I (that is, when n is different from 0) the resulting compound is a copolymer, whereas when B is absent (that is, when n is 0) the resulting compound is a homopolymer. Examples of possible meanings for B include, among others, 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide and vinyl acetate. Furthermore, monomer B can also be another polymerisable monomer carrying triflusal or HTB.

Although the present invention encompasses all the compounds mentioned above, a preferred group of compounds of the present invention are those polymeric compounds of formula I wherein the hydrolysable covalent bond is a carboxylic ester bond.

Another preferred group of compounds are those compounds of formula I wherein n represents 0.

Another preferred group of compounds are those compounds of formula I wherein n is different from 0.

A more preferred group of compounds of formula I are those polymeric compounds corresponding to relative formula **Ia**:



(Ia)

wherein: R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents $-COCH_3$ or hydrogen;

X represents $-(CH_2CH_2O)_p-$;

p represents an integer from 1 to 100; and

B, m and n have the previously described meaning.

A still more preferred group of compounds of the present invention are those compounds of formula **Ia** wherein R_1 represents methyl and p represents 1.

A particularly preferred group of compounds are those compounds of formula **Ia** wherein R_1 represents methyl; p represents 1 and n represents 0.

Another particularly preferred group of compounds are those compounds of formula **Ia** wherein R_1 represents methyl; p represents 1 and n is different from 0. Within this group of compounds, those compounds wherein B represents a residue of 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide or vinyl acetate are preferred, and those wherein B represents a residue of N,N-dimethylacrylamide are still more preferred; a compound particularly preferred within this class is that corresponding to a molar fraction where m is 0.2 and n is 0.8.

The molecular weight of the polymeric compounds of the present invention can vary within a broad range, being preferred for use as coatings for synthetic biomaterials those polymeric compounds of formula I with an average molecular weight between 10000 and 100000 Daltons.

The polymeric compounds of formula I can be prepared by any of the known methods of radical polymerization. For example, they can be prepared by polymerization in a solution of the desired monomer or monomers in a suitable solvent in the presence of a polymerization initiator.

As initiator any compound described in the literature for such purpose can be used, for example benzoyl peroxide, lauroyl peroxide, cumene peroxide, butyl perbenzoate, 2,2'-azobisisobutyronitrile or 2,2'-azobisisopentanoic acid, among which benzoyl peroxide and 2,2'- azobisisobutyronitrile are preferred. The amount of initiator to be used will depend upon the molecular weight that it is desired to obtain, and will be easily determined by those skilled in the art.

As examples of suitable solvents we can mention dioxane, dimethylformamide, isopropanol, dioxane/water mixtures, chloroform, dimethylsulfoxide, acetone and acetone/water mixtures, among which the use of polar solvents such as dimethylformamide or solvating solvents such as dioxane or dioxane/water mixtures rich in dioxane are preferred.

The reaction temperature will depend on the initiator used and will also determine the molecular weight of the resulting polymeric system, as will be known by those skilled in the art; in general, a temperature between 50 and 70°C will be suitable.

The time of polymerization required is not too long, due to the nature of the radical polymerization reactions and the fact that they are addition chain reactions; in general we have found that polymerization times between 6 to 24 hours are sufficient to reach high monomer to polymeric system conversions, although in some cases longer polymerization times might be necessary.

The polymers of formula I are finally isolated using conventional methods, for example by precipitation in a suitable solvent such as ethanol, methanol, isopropanol, hexane, heptane or diethyl ether. In general, it is advisable to use a high precipitant/solution ratio, that is of at least 10 times the volume of precipitant with regard to the volume of solution, to guarantee a good precipitation.

The acrylic or vinylic monomers carrying triflusal or HTB can be prepared in

general through the formation of the covalent bond between a suitable acrylic or vinylic derivative and triflusal or HTB, or a reactive derivative thereof, following similar procedures to those described in the literature for the preparation of said type of covalent bonds.

Processes for preparing triflusal or HTB are described in the US patent mentioned above (US 4,096,252).

As stated above, the polymeric compounds of the present invention can be used as coatings for synthetic biomaterials, improving the properties of said materials. Said coatings can be prepared in general by immersion of the surface to be coated in a diluted solution, for example 1-2% w/v, of the desired polymer in a suitable solvent such as dimethylformamide, water/ethanol mixtures or dioxane/ethanol mixtures.

Brief description of the figures:

Figure 1 shows the synthesis of the monomer carrying triflusal described in example 1;

Figure 2 shows the synthesis of the polymer described in example 2;

Figure 3 shows the ^{1}H (3A) and ^{13}C (3B) NMR spectra of the polymer of example 2;

Figure 4 shows the synthesis of the polymer described in example 3;

Figure 5 shows the ^{1}H (5A) and ^{13}C (5B) NMR spectra of the polymer described in example 3;

Figure 6 shows the release of HTB from polymer of example 3 in rat plasma following the method described in example 4.

The following examples are included herein to illustrate the preparation and uses of the compounds of the present invention. In any case they are to be understood as limiting the scope of the invention in any way.

Example 1: Preparation of 2-(methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate (THEMA)

The preparation of this compound is shown in the scheme of Fig. 1.

a) 2-Acetyloxy-4-(trifluoromethyl)benzoic acid chloride

In a round-bottomed flask 0.1 mols of triflusal are reacted with 70 mL of $SOCl_2$, the flask is connected to a refrigerant and the reaction is heated at reflux for 4 h, under magnetic stirring. Next, the unreacted $SOCl_2$ excess is removed by distillation, first at atmospheric pressure and then at reduced pressure. Then, the desired acid chloride is isolated by distillation at reduced pressure. The yield of the reaction is 64 %.

^{1}H-NMR (DMSO-d_6, 300 MHz, 20°C); δ: 8.1 (d, 1H, arom), 7.7 (d, 1H, arom), 7.6 (s, 1H, arom), 2.3 (s, 3H, CH_3COO-).

b) 2-(Methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate (THEMA)

In a flask are mixed 0.025 mols of 2-hydroxymethyl methacrylate (HEMA) and 5.21 mL Et_3N (0.025 mols) in 100 mL of diethylether as solvent. To this mixture, 0.025 mols of the acid chloride obtained in step a) dissolved in diethyl ether is added dropwise, under nitrogen flux and at room temperature. Once the acid chloride addition is complete, the reaction is kept under stirring for 24 hours. The precipitated triethylamine hydrochloride is removed by filtration. The filtrate is washed first with water containing some drops of concentrated HCl, and then with water several times. The aqueous phase is discarded and the organic phase is dried over anhydrous $MgSO_4$. Finally, ether is removed under vacuum until constant weight. The yield of the reaction is 52%.

^{1}H-NMR (DMSO-d_6, 300 MHz, 20°C); δ: 8.1 (d, 1H, arom), 7.8 (d, 1H, arom), 7.7 (s, 1H, arom), 6.1 and 5.7 (d, CH_2=C<), 4.6 and 4.4 (t,t, -CH_2-CH_2-), 2.3 (s, 3H, CH_3COO-), 1.9 (s, 3H, CH_3-C=).

The compound 2-(methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate, which is new and is a valuable intermediate for the preparation of compounds of the present invention, is also the object of the present invention.

Example 2: Preparation of poly[2-(methacryloyloxy)ethyl 2-acetyloxy-4-(trifluoromethyl)benzoate] (poly[THEMA])

This compound was prepared by polymerization of the monomer carrying triflusal obtained in example 1 (THEMA). The chemical structure of this compound and its synthesis are shown in the scheme of Fig. 2.

In Pyrex glass ampoules, 5 g of THEMA (obtained in example 1) is dissolved in 28 mL of a (4:1) purified dioxane/acetone mixture, the concentration

of the solution thus being 0.5M. Next, benzoyl peroxide (1.5×10^{-2} M) is added as the initiator; for the solution described above 100.8 mg are used. Oxygen is then removed from the solution by bubbling nitrogen (30 min) twice.

The sealed ampoules are immersed in a thermostatic bath at 60°C for 24 h. After polymerization, the polymer is precipitated by pouring it into an excess of ethanol; to precipitate 5 g of polymer 500 mL of ethanol is used, to which the polymer solution is added dropwise. This operation is carried out in an ice bath. The solution is kept under stirring for 4 h and is then filtered under vacuum. The precipitate thus obtained is washed several times with ethanol, is filtered again, and is then dried under vacuum until constant weight. The yield of the reaction is 90%.

The average molecular weight of this polymer, determined by Gel Permeation Chromatography (GPC), is 48000 Daltons, with a polydispersity index M_w/M_n of 1.8.

The ^1H (400 MHz, $CDCl_3$, 45°C) and ^{13}C (100 MHz, DMSO-d_6, 45°C) NMR spectra of the polymeric compound obtained in this example are shown in Fig. 3 (A and B).

Example 3: Preparation of a copolymer from THEMA and N,N-dimethylacrylamide (DMA) (poly[THEMA-co-DMA])

The chemical structure of this copolymer and its synthesis are shown in the scheme of Fig. 4.

1 g of THEMA (obtained in example 1) and 1 g of DMA is dissolved in 25.75 mL of purified dioxane (0.5 M). Next, 46.75 mg of benzoyl peroxide at a concentration of 1.5×10^{-2} M is added and oxygen is removed from the solution by bubbling nitrogen twice for 30 minutes.

The sealed ampoule is immersed in a thermostatic bath at 60°C for 24 h. The polymer is then precipitated by pouring the resulting solution dropwise into 1 L of diethyl ether. The solution is kept under stirring for 4 h, diethyl ether is then removed by decantation and the precipitate is dried under vacuum until constant weight. The yield of the reaction is 80%.

^1H-NMR analysis showed that this copolymer contains a 52 wt % of THEMA with a m/n molar fraction of 0.2/0.8. GPC determination showed that the average molecular weight was 33000 Daltons.

^{1}H (200 MHz, $CDCl_3$, 40°C) and ^{13}C (100 MHz, $CDCl_3$, 45°C) NMR spectra of the polymeric compound obtained in this example are shown in Fig. 5 (A and B).

Example 4: Study of the release of the antiaggregating compound contained in a polymer of formula I in rat plasma

The release of the antiaggregating agent from the polymers of the present invention can be assessed using an *in vitro* assay comprising the incubation at 37° C and under constant stirring of rat plasma to which a solution of the desired polymer has been added and then determine at different times the release of the drug by HPLC. In parallel, and in order to check the linearity and accuracy of the method, the same assay was performed using stock solutions of the drug.

a) Plasma preparation

Rat plasma is obtained by cardiac puncture. Animals are placed in a chamber previously saturated with diethyl ether; when animals are anesthetized, they are placed in ventral position and are fastened to a table in order to carry out a cardiac puncture through the intercostal space. Blood is transferred to polypropylene tubes containing 20% of 3.2% sodium citrate as anticoagulant, tubes are closed and homogenized manually. Plasma is then obtained by blood centrifugation at 2000 g.

b) Solution preparation

For this assay, the polymer obtained in example 3 was used. This polymer carries triflusal. In this case, due to the well-known hydrolysis of triflusal in aqueous media to give its metabolite, HTB, the release of HTB was followed by HPLC.

The powdered polymer is dissolved in methanol and solutions having a concentration of 0.96 mg/mL, equivalent to a total HTB concentration of 1.4 mM, are prepared. In parallel, the same assay is performed using HTB stock solutions in order to obtain a suitable calibration curve. The concentrations of HTB used are: 1.25 mM, 1.5 mM, 6.2 mM and 9.3 mM.

c) Release assay

The rat plasma obtained as described in step a) is divided into 0.2 mL volumes which are distributed in polypropylene tubes. To each tube, 10 µL of the polymer solution is added. Tubes are immersed in a bath at 37 °C under constant

stirring. Aliquotes are collected at different times and are analyzed by HPLC, using the following conditions:

- Waters μBoundapak C-18 column of 3.9x300 mm;
- Perkin Elmer LC-250 pump;
- UV/Vis detector Perkin-Elmer LC-95; λ = 305 nm.
- Waters 770 Data Module integrator
- Mobile phase: aqueous solution of Pic A- methanol, 60:40, microfiltered and degassed.

Before HPLC analysis, samples are prepared by precipitating plasmatic proteins with methanol 1:5, followed by centrifugation at 15000 rpm for 10 min. The supernatant is mixed with an identical volume of mobile phase, microfiltered and injected into the chromatograph.

d) Results

The results obtained in this assay are shown in figure 6, wherein a time-dependent release of HTB from the polymer obtained in example 3 is observed.

Example 5: Example of the preparation of a Goretex prostheses coated with a polymer of formula I

Commercial Goretex® vascular grafts are immersed into a 1:1 dioxane/ethanol solution of the polymer of example 2 (2 wt %) for 30 min. The wet segments of the prostheses are dried at room temperature in a controlled atmosphere of nitrogen until constant weight. The thickness and quantity of the coating is determined by measuring the weight gain of the coated prostheses with respect to the original uncoated prostheses. Homogeneous coatings having a thickness of about 3-5 μm are obtained.

Example 6: In vitro assessment of the thrombogenic properties of a synthetic biomaterial coated with a polymer of the invention

The effect of the application of a polymer of the invention as coating of a synthetic biomaterial upon the thrombogenic properties of said material can be evaluated by measuring the platelet aggregation on prostheses coated with a polymer of the invention in comparison to that observed in the uncoated material; platelet aggregation can be monitored by determining the amount of platelets retained in the material or by scanning electron microscopy (SEM).

a) Method

For this study, platelet-rich plasma (PRP) from sheep arterial blood is used. PRP is isolated by centrifugation of 40 mL blood at 1500 rpm for 10 min. After this time, the supernatant is discarded and the content of platelets is determined with a hematologic counter Serono-3000. The prostheses used in this assay are Goretex® vascular grafts of 4 mm inner diameter. A group of prostheses coated with a polymer and a control group (uncoated prostheses) is used.

Prostheses are mounted on seeding chambers and 100 μL of PRP is added. Chambers are incubated at 37 °C in an incubator (5% CO2) during different periods of time. After the assay time, prostheses are washed three times with MEM (Minimal Essential Medium) to remove non-retained platelets and the number of platelets retained in the prostheses in comparison with the control group is determined indirectly by counting the number of platelets recovered at each of the assay times.

After this, samples are fixed with glutaraldehyde, washed with buffered solution (pH 7.4), dehydrated in a graded acetone series and metallized with gold/palladium for their examination by SEM using a scanning electron microscope Zeiss 950 DSM.

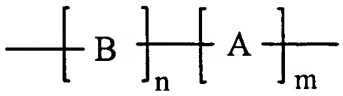
b) Results

Using this assay, it has been observed that the coating of Goretex® prostheses with a thin layer of the polymer obtained in example 2 following the method disclosed in example 5 decreases the retention of platelets in comparison with the uncoated prostheses. In addition, the analysis by SEM shows that platelets are less aggregated in the case of coated prostheses, while the uncoated prostheses (control group) present coagulated domains of aggregated platelets with a strong adhesion to the porous structure of the surface of Goretex®.

These results show the utility of the polymers of the invention to improve the thrombogenic properties of synthetic biomaterials.

CLAIMS

1.- A polymeric compound of relative general formula **I**



(I)

wherein:

A represents a residue of a polymerisable acrylic or vinylic monomer carrying triflusal or HTB, wherein triflusal or HTB are linked to the remainder of the monomer molecule through an *in vivo* hydrolizable covalent bond;

B represents a residue of a second polymerisable monomer;

m and n represent the molar fractions of the monomers A and B in the polymer so that m + n is always 1 and m is always different from 0;

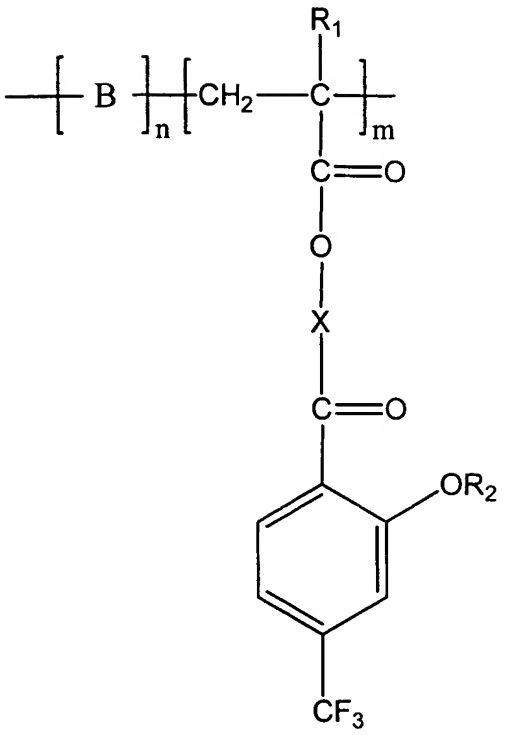
and wherein the A and B units are distributed randomly in the polymer.

2.- A compound according to claim 1 wherein the hydrolysable covalent bond is a carboxylic ester bond.

3.- A compound according to claim 1 wherein n represents 0.

4.- A compound according to claim 1 wherein n is different from 0.

5.- A compound according to claim 1 of relative formula **Ia**:



(Ia)

wherein: R_1 represents hydrogen or C_{1-4} alkyl;

R_2 represents $-COCH_3$ or hydrogen;

X represents $-(CH_2CH_2O)_p-$;

p represents an integer from 1 to 100; and

B, m and n have the meaning described in claim 1.

6.- A compound according to claim 5 wherein R_1 represents methyl and p represents 1.

7.- A compound according to claim 6 wherein n represents 0.

8.- A compound according to claim 6 wherein n is different from 0.

9.- A compound according to claim 8 wherein B represents a residue of 2-hydroxyethyl methacrylate, methyl methacrylate, methyl acrylate, vinylpyrrolidone, acrylic acid, methacrylic acid, acrylamide, N,N-dimethylacrylamide or vinyl acetate.

10.- A compound according to claim 9 wherein B represents a residue of N,N-dimethylacrylamide.

11.- A compound according to claim 10 wherein m is 0.2 and n is 0.8.

12.- A compound according to any of the preceding claims having an average molecular weight between 10000 and 100000 Daltons.

13.- A compound according to claim 7 wherein R_2 represents $-COCH_3$.

14.- A compound according to claim 13 having an average molecular weight of 48000 Daltons and ^{1}H and ^{13}C NMR spectra in accordance with the ones shown on figure 3.

15.- A compound according to claim 11 wherein R_2 represents $-COCH_3$.

16.- A compound according to claim 15 with an average molecular weight of 33000 Daltons and ^{1}H and ^{13}C NMR spectra in accordance with the ones shown on figure 5.

17.- A process for the preparation of a polymeric compound of formula I according to claim 1 which comprises the radical polymerization of a monomer A and optionally a second monomer B in the molar fractions m and n, respectively, wherein A, B, m and n have the meaning described in claim 1, in the presence of a polymerization initiator, in a suitable solvent.

18.- Use of a polymeric compound of formula I according to any of claims 1 to 16 as coating for synthetic biomaterials.

19.- Use according to claim 18 wherein the synthetic biomaterial is a vascular prosthesis or an artificial cardiac valve.

20.- Use of triflusal or HTB for the preparation of biocompatible polymeric compounds for coating synthetic biomaterials.

21.- Use according to claim 20 wherein the synthetic biomaterial is a vascular prosthesis or an artificial cardiac valve.

22.- A synthetic biomaterial coated with a polymer carrying triflusal or HTB of formula I according to any of claims 1 to 16.

23.- A synthetic biomaterial according to claim 22 which is a vascular prosthesis or an artificial cardiac valve.

24.- Use of a polymeric compound of formula I according to any of claims 1 to 16 as a controlled delivery system for triflusal or HTB.

25.- The compound 2-(methacryloyloxy)ethyl 2-(acetyloxy)-4-(trifluoromethyl)benzoate.

Fig. 1

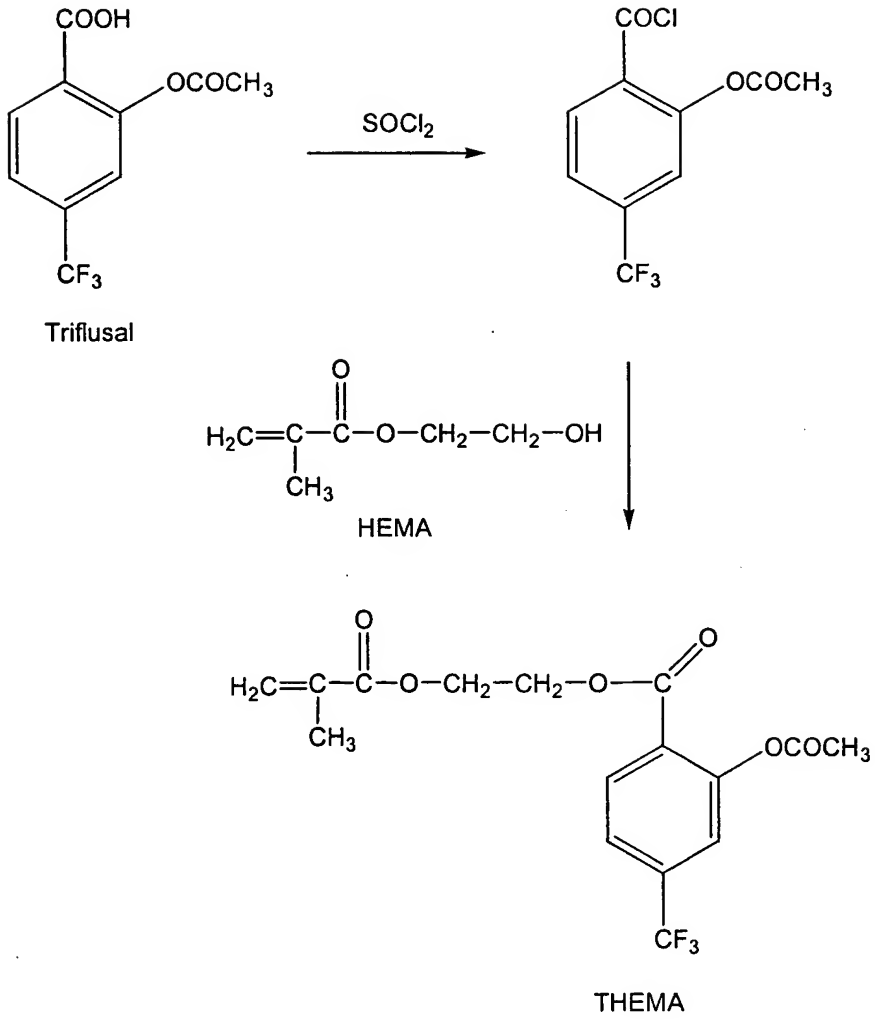
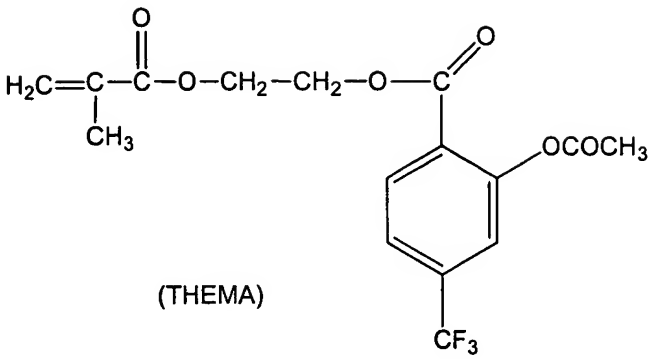
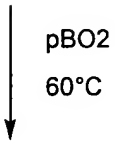
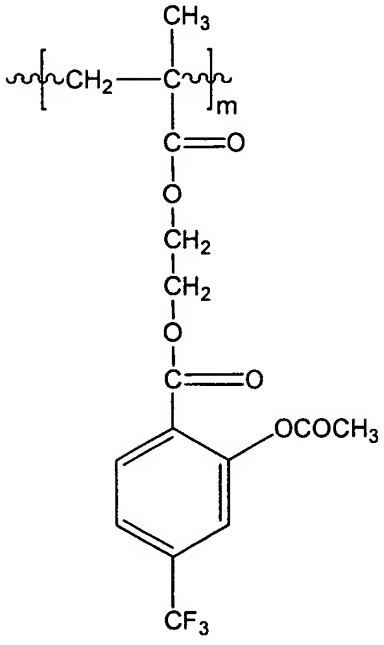

COOH
OCOCH3
CF3
SOCl2
COCl
OCOCH3
CF3
Triflusal
O
H2C=C-C-O-CH2-CH2-OH
CH3
HEMA
O
H2C=C-C-O-CH2-CH2-O-C
O
CH3
OCOCH3
CF3
THEMA

Fig. 2



(THEMA)





poly[THEMA]

Fig. 3A

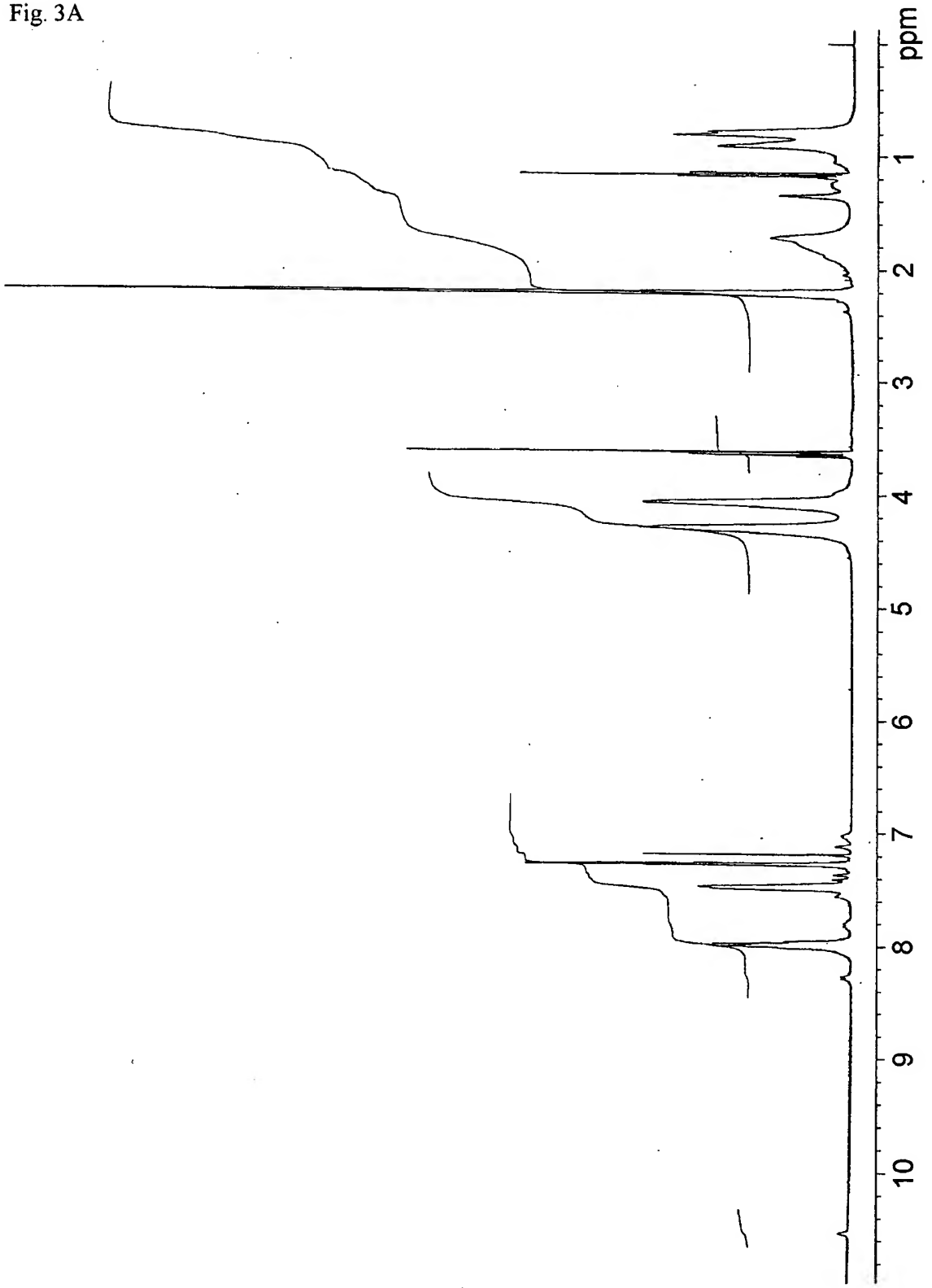


Fig. 3B

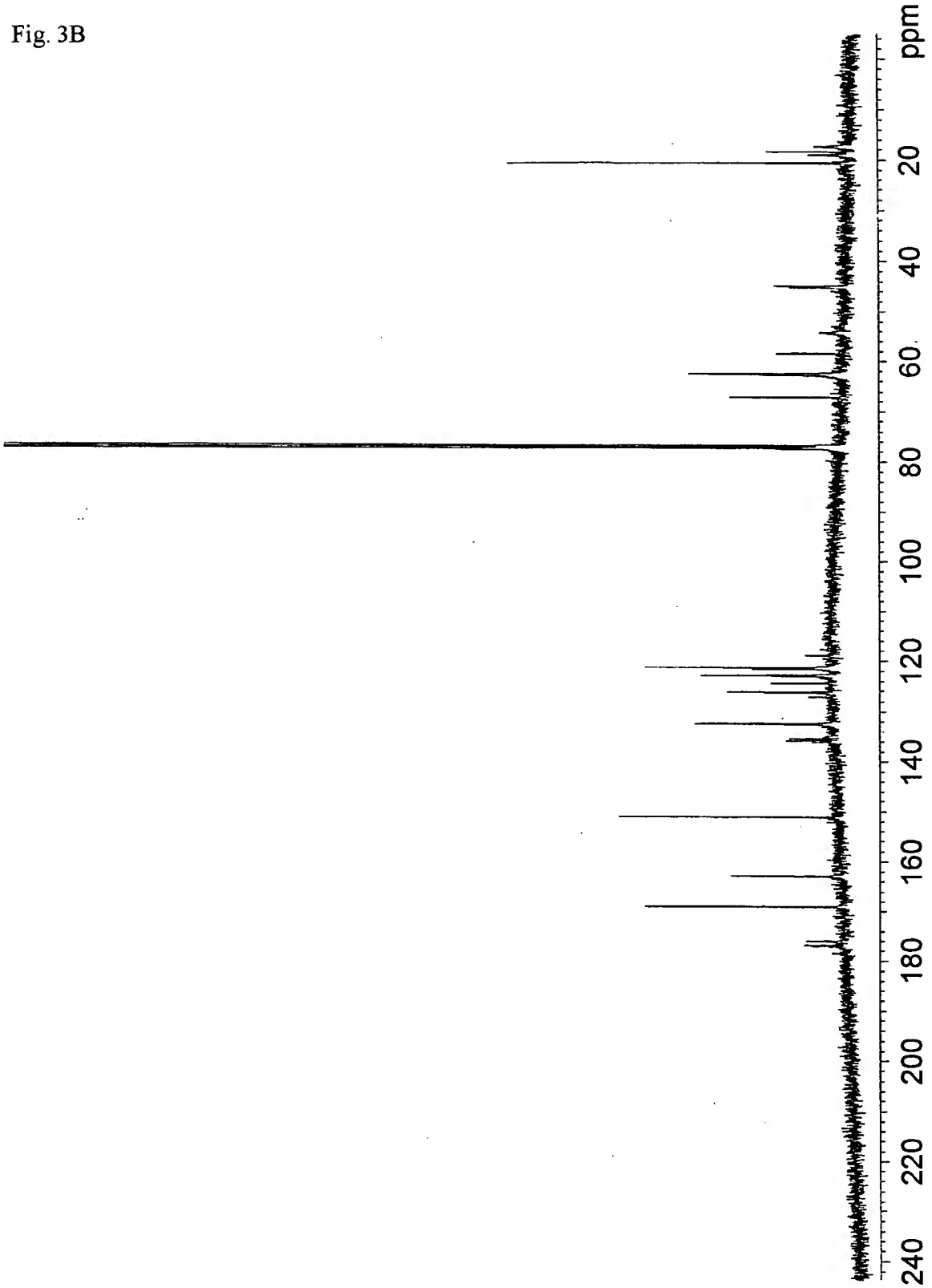


Fig. 4

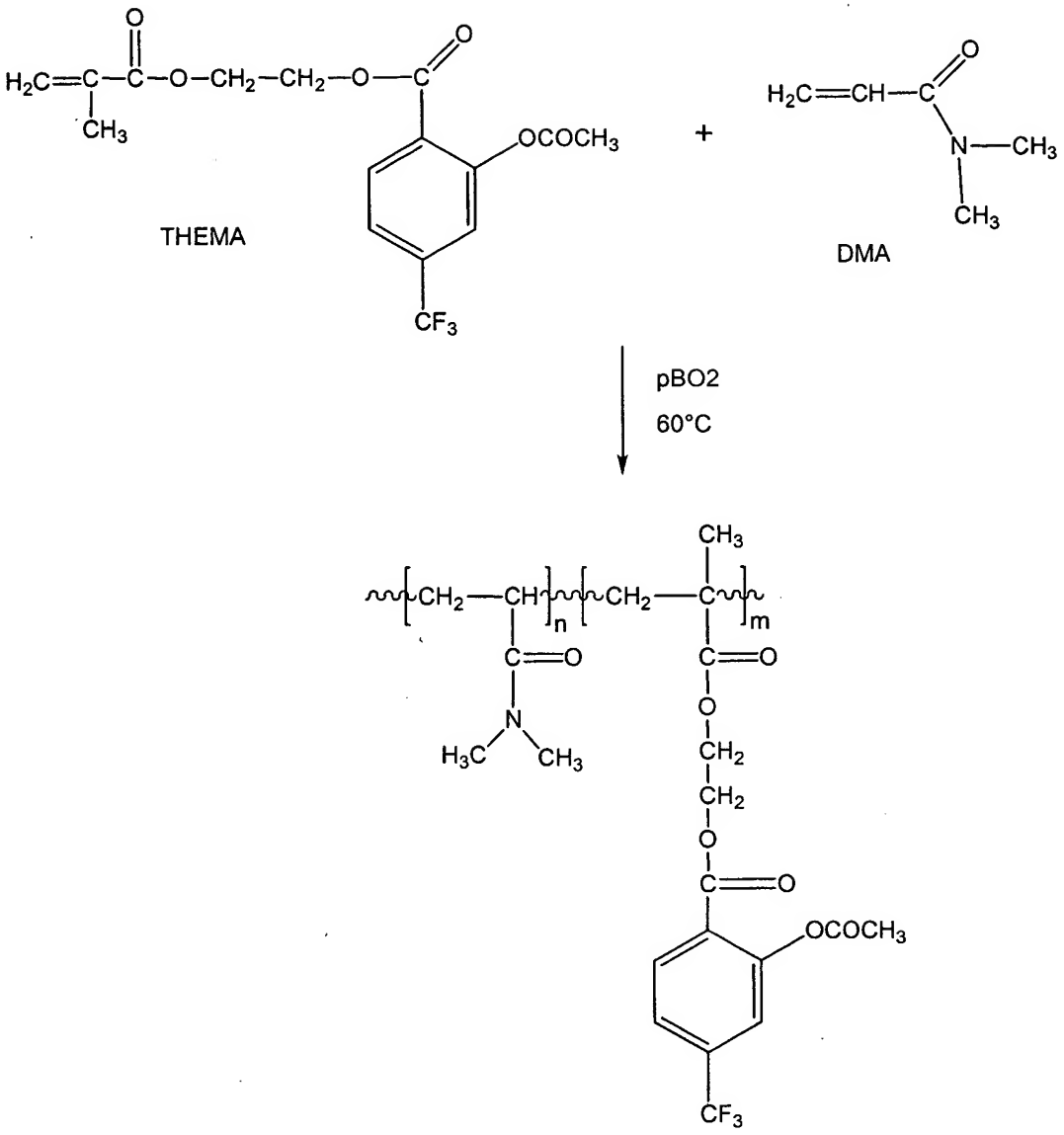


Fig. 5A

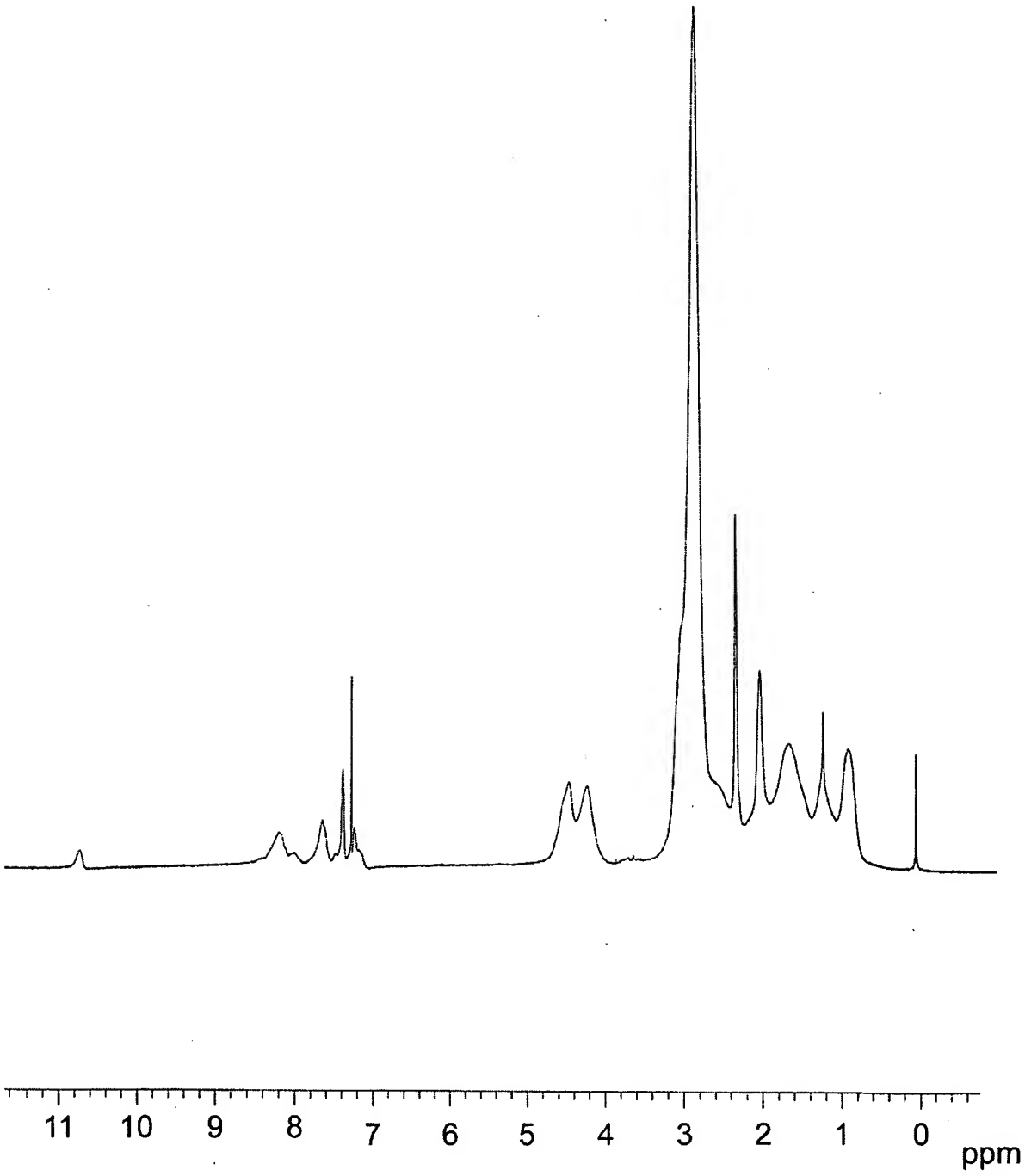


Fig. 5B

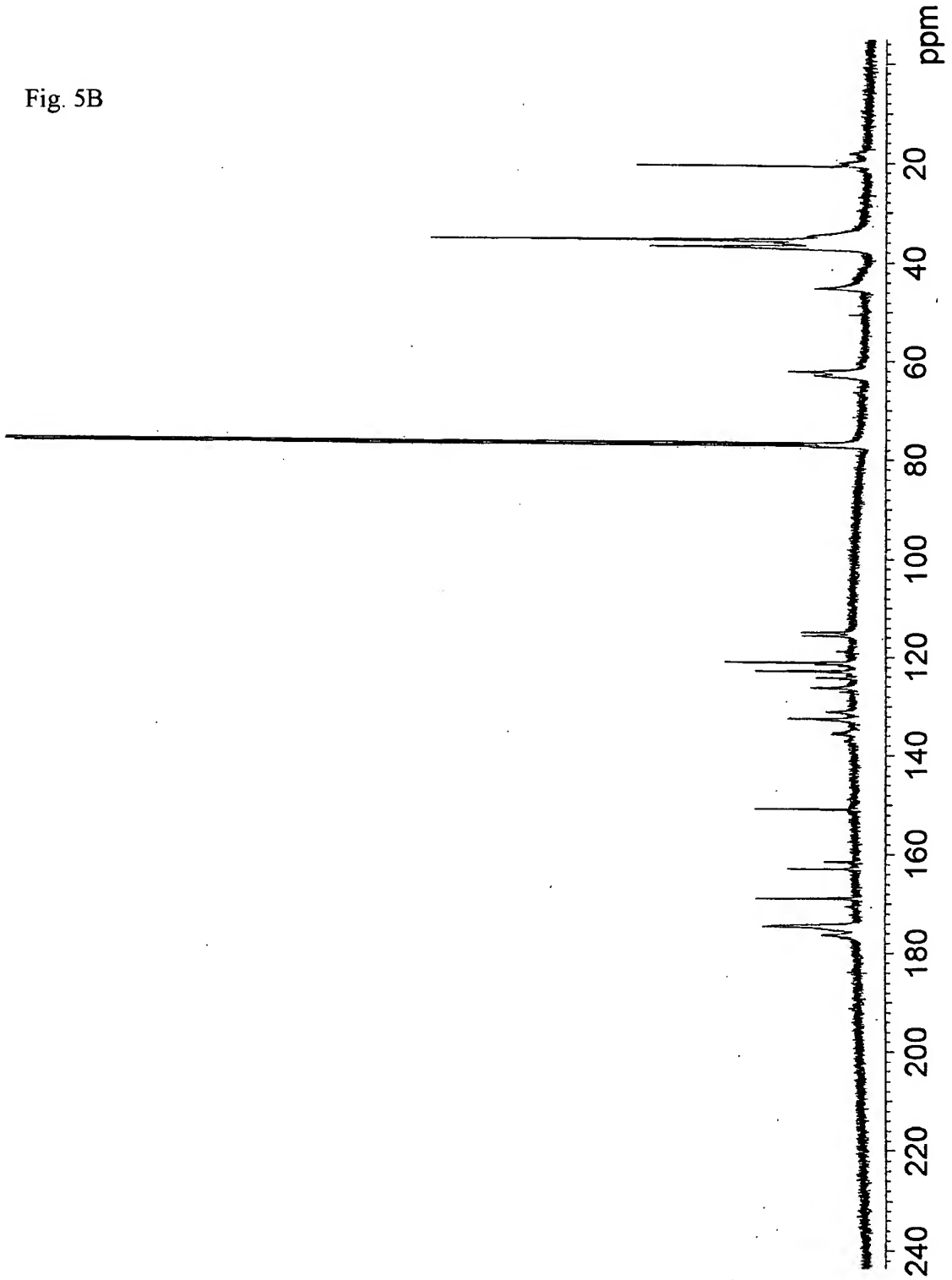
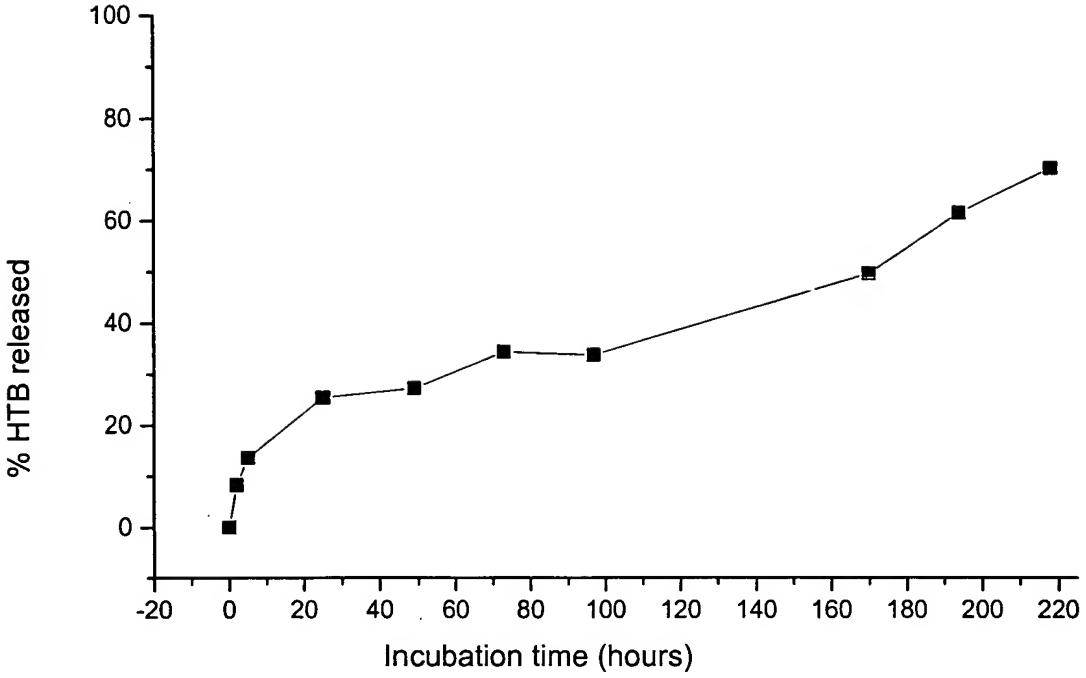


Fig. 6


% HTB released
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
140
160
180
200
220
Incubation time (hours)

Abstract

New biocompatible polymeric systems carrying triflusal or HTB are described which result from the polymerization of a monomer A of the acrylic or vinylic type and carrying triflusal or HTB, wherein triflusal or HTB are linked to the remainder of the molecule of said monomer through an *in vivo* hydrolysable covalent bond, and optionally a second polymerisable monomer B. These new polymeric systems are useful as coating for synthetic biomaterials.